SISCR Module 7

Part III:
Comparing Two Risk Models

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Outline of Part III

1. How to compare two risk models
2. How to assess the incremental value of a new biomarker
3. How not to assess the incremental value of a new biomarker

1. How to compare two risk models

In a nutshell:

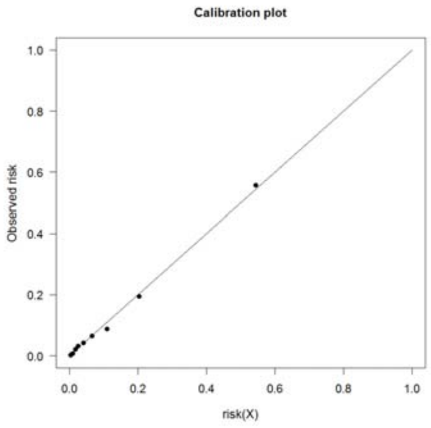
- What is your preferred measure(s) for evaluating a single risk model?
- Compare that measure(s) for two risk models.

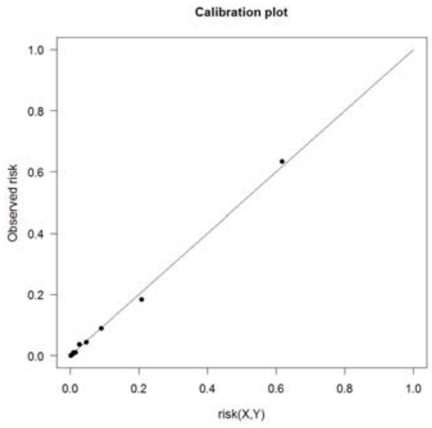
Example

- risk(X) and risk(X,Y) for data from DABS
- Both models are very well calibrated (moderate calibration criterion):

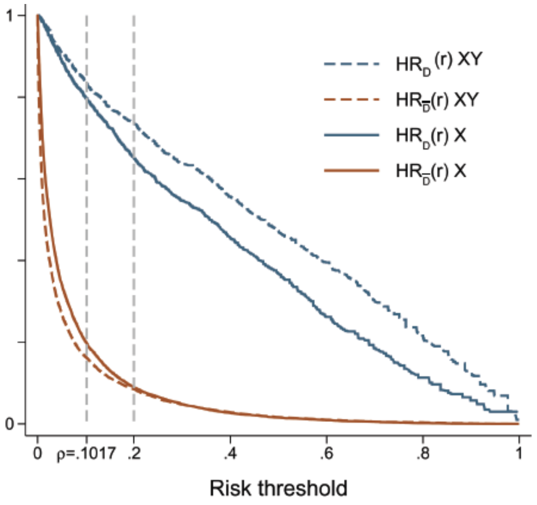
P(D=1 | predicted risk r) ≈ r

(moderate calibration criterion)



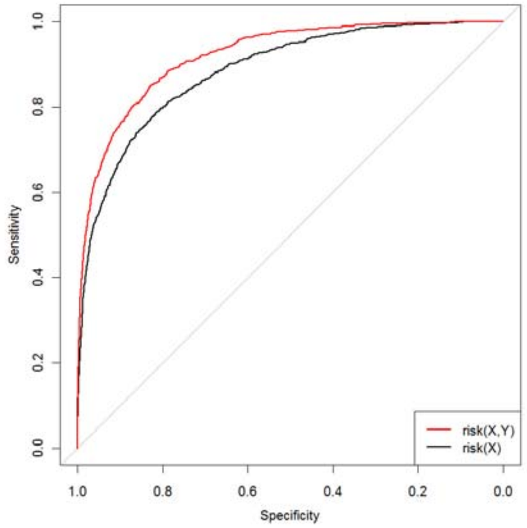


High risk classification for cases and controls

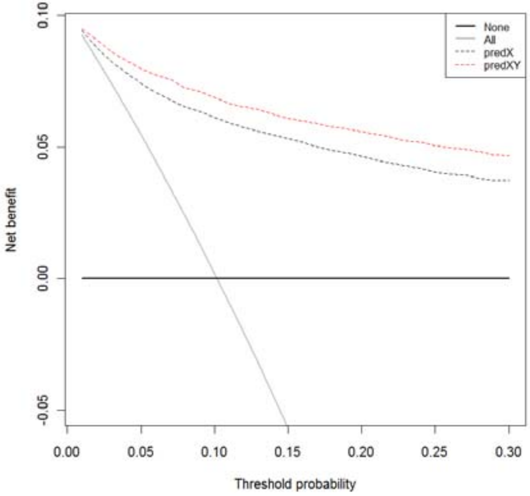


$\rho = 0.1017$

Compare ROC Curves



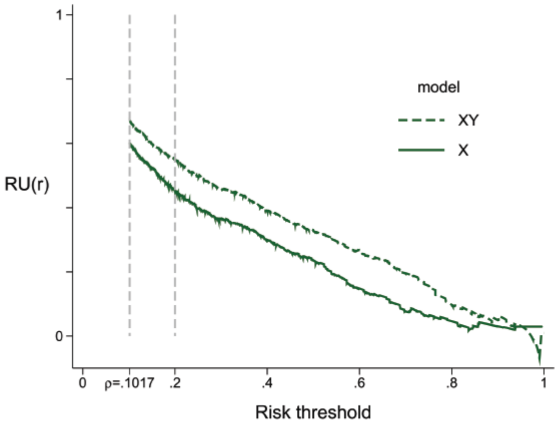
Decision Curves – compare the NB of risk(X) and risk(X,Y)



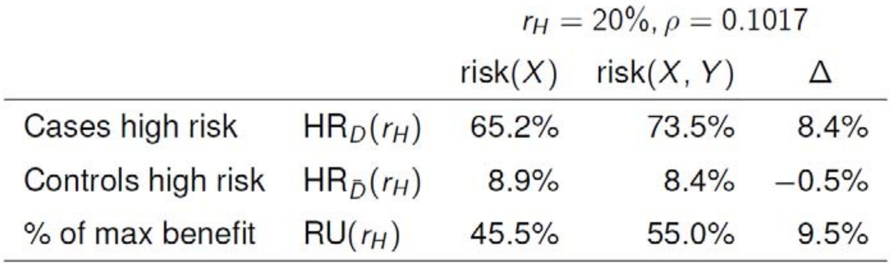
(Also Recall: Prostate Cancer Example in Section 2b)

Relative utility plots – compare the Relative Utility of risk(X) and risk(X,Y)

$\rho = 0.1017$



Most appealing summary measures



		$r_H = 20\%, \rho = 0.1017$		
		risk(X)	risk(X, Y)	Δ
Cases high risk	$\mathrm{HR}_D(r_H)$	65.2%	73.5%	8.4%
Controls high risk	$\mathrm{HR}_{\bar{D}}(r_H)$	8.9%	8.4%	-0.5%
% of max benefit	$\mathrm{RU}(r_H)$	45.5%	55.0%	9.5%

Less appealing summary measures

	risk(X)	risk(X,Y)	Δ	comments
AUC	0.884	0.920	0.036	ΔAUC is most popular metric
MRD	0.322	0.416	0.094*	ΔMRD is also known as IDI
AARD	0.599	0.673	0.074	
ROC(0.20)	0.672	0.758	0.087	Sensitivity at fixed specificity

2. Incremental Value of New Biomarkers

- *Incremental Value* or *Prediction Increment*: the improvement in prediction from using a new marker in addition to existing markers.
- Kattan (2003): "Markers should be judged on their ability to improve an already optimized prediction model."

A common approach: 2-stage approach for evaluating incremental value

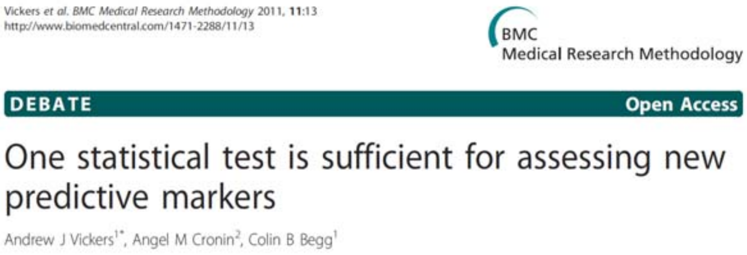
- Use a regression model to estimate P(D| X, Y) where X is the established predictor(s) and Y is the new marker

  e.g., $\text{logit } P(D=1|X, Y)=\beta_0+\beta_X X+\beta_Y Y$

  Test H_0: $\beta_Y = 0$
- If the null hypothesis is rejected, then examine $AUC_{X,Y}$ and test

  $$H_0: AUC_{X,Y} = AUC_X$$

Empirical argument against the two-stage approach:



Vickers *et al. BMC Medical Research Methodology* 2011, **11**:13
http://www.biomedcentral.com/1471-2288/11/13

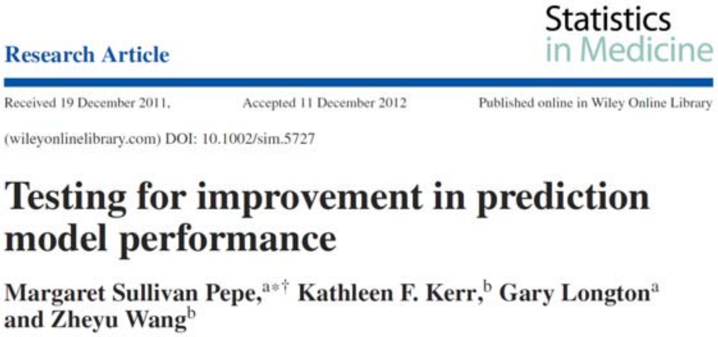
BMC
Medical Research Methodology

DEBATE **Open Access**

One statistical test is sufficient for assessing new predictive markers

Andrew J Vickers[1*], Angel M Cronin[2], Colin B Begg[1]

Theoretical argument:



Research Article

Statistics in Medicine

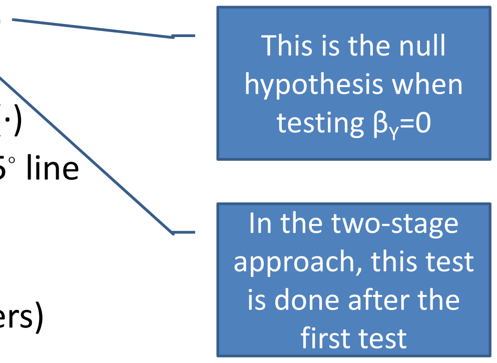
Received 19 December 2011, Accepted 11 December 2012 Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/sim.5727

Testing for improvement in prediction model performance

Margaret Sullivan Pepe,[a*†] Kathleen F. Kerr,[b] Gary Longton[a] and Zheyu Wang[b]

Equivalent Null Hypotheses

- Pepe *et al* (2013) prove the following null hypotheses are equivalent:
  - risk(X,Y)=risk(X)
  - $\text{AUC}_{X,Y}=\text{AUC}_X$
  - $\text{ROC}_{X,Y}(\cdot)=\text{ROC}_X(\cdot)$
  - $\text{ROC}_{Y|X}$ is the 45° line
  - IDI = 0
  - $\text{NRI}^{>0}=0$
  - (and a few others)

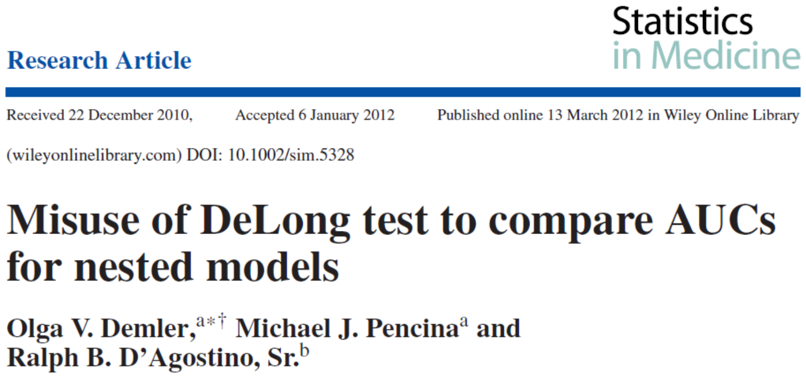


This is the null hypothesis when testing $\beta_Y=0$

In the two-stage approach, this test is done after the first test

- To say that these null hypotheses are the same is NOT to say that the associated statistical tests are the same.
- However, it doesn't make sense to test the same null hypothesis twice.
  - first, with a well-developed, powerful test
  - second, with an under-developed test with poor power (p-value from software should not be trusted, may be excessively conservative)
  - Illogical scientific approach

More details about why the AUC-based test is wrong:



Research Article

Statistics in Medicine

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Misuse of DeLong test to compare AUCs for nested models

Olga V. Demler,[a*†] Michael J. Pencina[a] and Ralph B. D'Agostino, Sr.[b]

- Hypothesis testing has very limited value
  - much more important to quantify the improvement offered by the new predictor
  - the strength of evidence to establish whether a new predictor is useful far exceeds what is needed to establish statistical significance

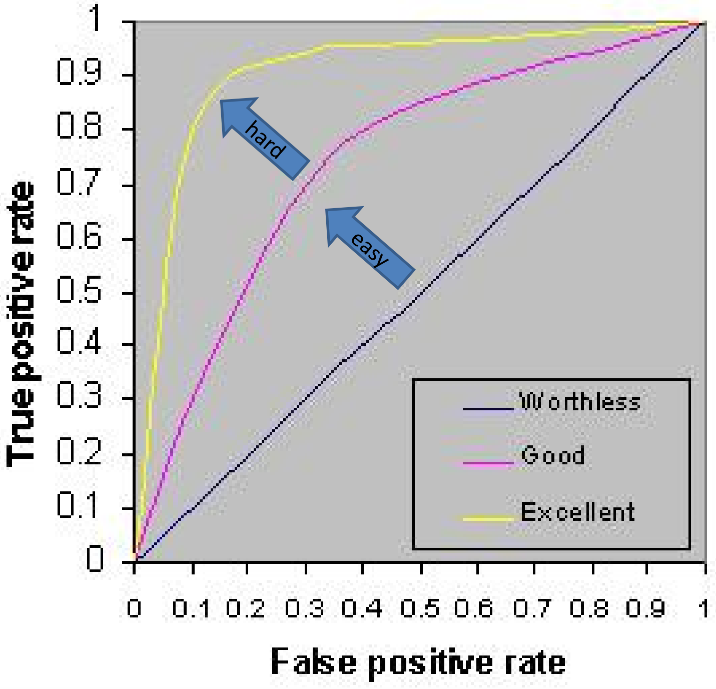
Testing Vs. Estimation

- A statistical test examines the evidence that a marker has *any* incremental value.
- However, the real challenge is finding markers that offer clinically important improvements in prediction.
- Quantifying incremental value is much more important (and more challenging) than hypothesis testing.
  - This comes down to deciding how we value a risk model

3. How not to assess incremental value

- Most common approach is to examine increase in AUC
- Since AUC is not a clinically meaningful measure, how do we know whether the increase in AUC is “enough”?

- ΔAUC (AUC$_{X,Y}$ compared to AUC$_X$). Some investigators consider this metric to be “insensitive” (Cook, 2007)
  - This might mean that a favorite biomarker produced a disappointing ΔAUC.
  - “Sensitivity” of ΔAUC is probably not the problem. The real problems are
    - The scale of AUC is such that an increase of 0.02 is “large”
    - p-values computed for ΔAUC are wrong; incorrect methodology tends to produce too-large p-values
    - It’s fundamentally hard to improve upon a risk model that has moderately good predictive ability



A new approach: Reclassification
(Cook, *Circulation* 2007)

- Proposed that a new marker is useful if it re-classifies lots of people
  - reclassification table, next slide

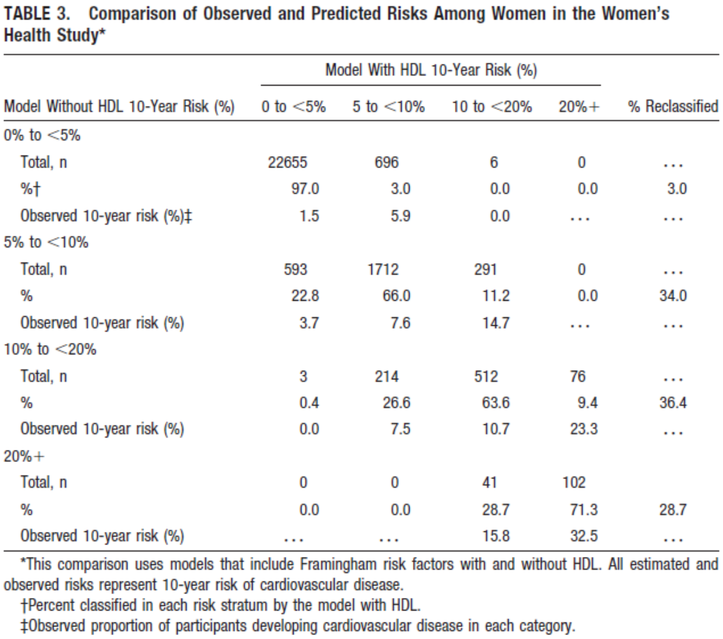


TABLE 3. Comparison of Observed and Predicted Risks Among Women in the Women's Health Study*

	Model With HDL 10-Year Risk (%)				
Model Without HDL 10-Year Risk (%)	0 to <5%	5 to <10%	10 to <20%	20%+	% Reclassified
0% to <5%					
Total, n	22655	696	6	0	. . .
%†	97.0	3.0	0.0	0.0	3.0
Observed 10-year risk (%)‡	1.5	5.9	0.0	. . .	. . .
5% to <10%					
Total, n	593	1712	291	0	. . .
%	22.8	66.0	11.2	0.0	34.0
Observed 10-year risk (%)	3.7	7.6	14.7	. . .	. . .
10% to <20%					
Total, n	3	214	512	76	. . .
%	0.4	26.6	63.6	9.4	36.4
Observed 10-year risk (%)	0.0	7.5	10.7	23.3	. . .
20%+					
Total, n	0	0	41	102	
%	0.0	0.0	28.7	71.3	28.7
Observed 10-year risk (%)	. . .	. . .	15.8	32.5	. . .

*This comparison uses models that include Framingham risk factors with and without HDL. All estimated and observed risks represent 10-year risk of cardiovascular disease.

†Percent classified in each risk stratum by the model with HDL.

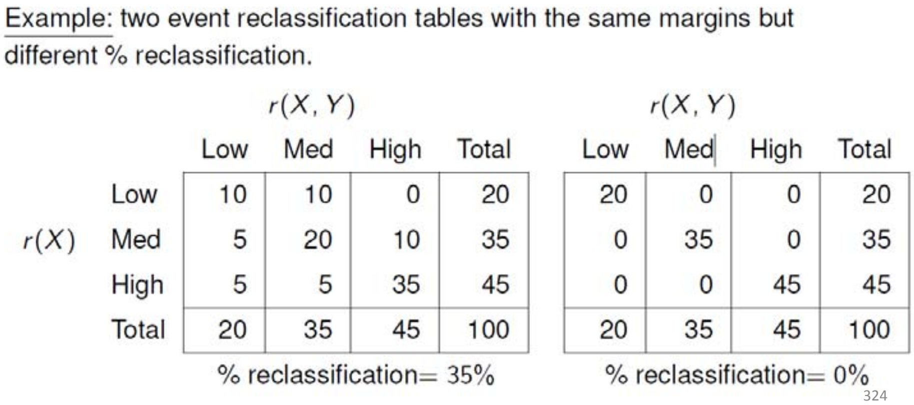
‡Observed proportion of participants developing cardiovascular disease in each category.

Reclassification Tables: Considerations

- Original proposal did not account for whether reclassification was in the "correct" direction
- Does not teach us about the performance of either risk(X) or risk(X, Y)
  - "inherently comparative"
- If presented separately for cases and controls, the reclassification table can be very interesting
  - but doesn't directly help us assess the incremental value of the new biomarker

Reclassification Tables: Considerations

- Lots of reclassification does not imply improved performance.



Example: two event reclassification tables with the same margins but different % reclassification.

		$r(X,Y)$			
		Low	Med	High	Total
	Low	10	10	0	20
$r(X)$	Med	5	20	10	35
	High	5	5	35	45
	Total	20	35	45	100

% reclassification= 35%

$r(X,Y)$			
Low	Med	High	Total
20	0	0	20
0	35	0	35
0	0	45	45
20	35	45	100

% reclassification= 0%

Net Reclassification Index (NRI)

- Proposed in 2008
  - Pencina, D’Agostino, D’Agostino, Vasan, *Statistics in Medicine*, 2008
- Followed on the heels of Cook’s paper
- NRI is really a family of statistics

NRI terminology

event	person with the condition or destined to have the condition (“case”)
nonevent	not an event (“control”)
old	risk model with established predictors (“baseline”)
new	risk model with established predictors and new predictor (“expanded”)

Net Reclassification Improvement (NRI)

NRI = P(up | event) - P(down | event) + P(down | nonevent) - P(up | nonevent)

“up” means an individual moves to a higher risk category
“down” means an individual moves to a lower risk category

Original NRI (categorical NRI): apply this formula to fixed risk categories

Net Reclassification Improvement (NRI)

The *NRI* is the sum of the “event *NRI*” and the *“*nonevent *NRI”*:

$$\mathrm{NRI}_e = P(\text{ up } | \text{ event }) - P(\text{ down } | \text{ event })$$

$$\mathrm{NRI}_{ne} = P(\text{ down } | \text{ nonevent }) - P(\text{ up } | \text{ nonevent })$$

Fixed Risk Categories

Two Risk categories: Low Risk, High Risk

Three Risk categories: Low, Medium, High Risk

4 Risk categories: (Cook paper, for example)

Net Reclassification Improvement (NRI)

$$\text{NRI} = \underbrace{\text{P(up | event) - P(down | event)}}_{\text{NRI}_{e}^{>0}} + \underbrace{\text{P(down | nonevent) - P(up | nonevent)}}_{\text{NRI}_{ne}^{>0}}$$

The ``category-free NRI'' interprets this formula for any upward or downward movement in predicted risk. Denote $\text{NRI}^{>0}$

Interpreting NRI: NRI is not a proportion

NRI = P(up | event) - P(down | event) + P(down | nonevent) - P(up | nonevent)

NRI is a linear combination of four proportions.

Theoretical maximum value is 2.

Can be negative.

Interpreting NRI

In contrast to the NRI, the "event *NRI*" and *"*nonevent *NRI*" have straightforward interpretations.

$$NRI_e = P(\text{ up } | \text{ event }) - P(\text{ down } | \text{ event })$$

$$NRI_{ne} = P(\text{ down } | \text{ nonevent }) - P(\text{ up } | \text{ nonevent })$$

- •differences in proportions
- •NRI_e is the net proportion of events assigned a higher risk or risk category
- •NRI_{ne} is the net proportion of nonevents assigned a lower risk or risk category
- •"**net**" is an important word

Why the simple sum of NRI_e and NRI_{ne}?

$$NRI = P(\text{ up } | \text{ event }) - P(\text{ down } | \text{ event }) + P(\text{ down } | \text{ nonevent }) - P(\text{ up } | \text{ nonevent })$$

- •If they must be combined, then weighting by the population prevalence makes more sense.
- •… or a weighting that accounts for the costs of a misclassification
- •But why combine at all?
  - –NRI_e gives information about events
  - –NRI_{ne} gives information about nonevents

CACS in MESA

$$NRI^{0.1} = 0.164$$

CACS in MESA

$$NRI^{0.1} = 0.164$$

$$\text{However:}$$

$$NRI_e^{0.1} = 0.191$$

$$NRI_{ne}^{0.1} = -0.027$$

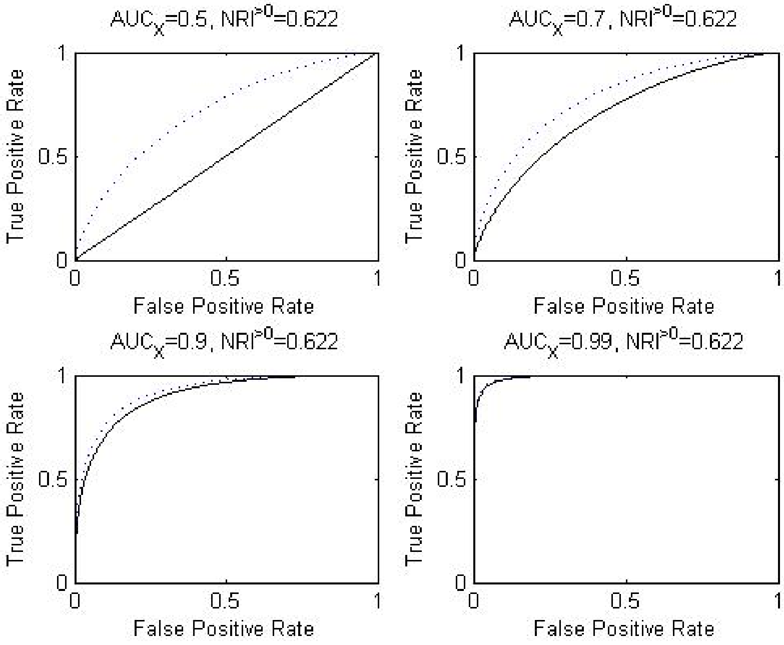
The nonevent NRI is negative, most subjects are nonevents, yet overall NRI is positive.

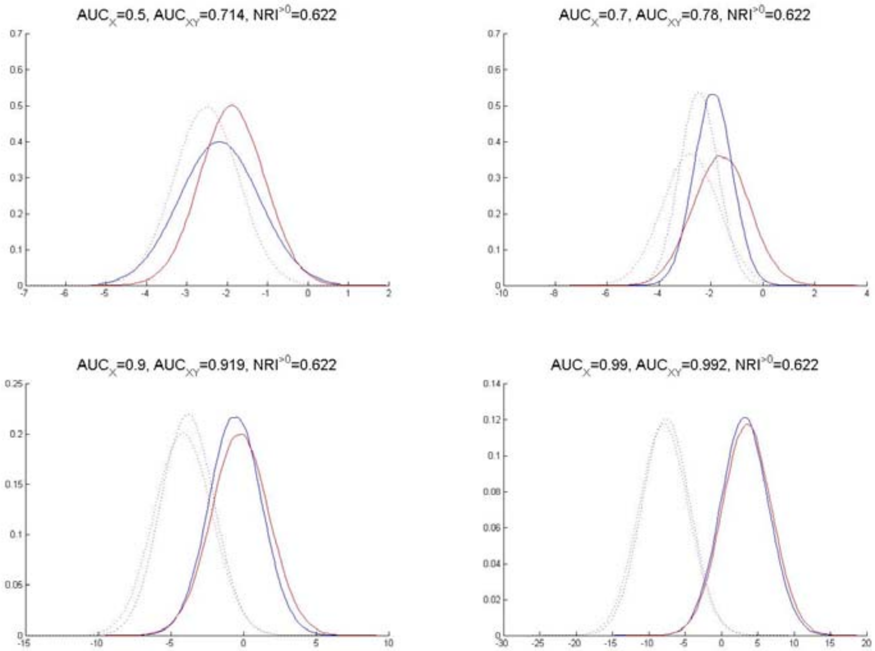
Using the prevalence 3.6%, the weighted sum is -0.020

Large and small values for NRI$^{>0}$ are undefined

"Further research is needed to determine meaningful or sufficient degree of improvement" in NRI$^{>0}$

– Pencina et al, *American Journal of Epidemiology* 2012





NRI$^{>0}$ does not contrast model performance measures

Measure	Baseline Model	Expanded Model	Prediction Increment for CACS
AUC	0.76	0.81	0.05
Mean Risk Difference (Cases vs. Controls)	0.03	0.06	0.03
NRI$^{>0}$	NA	NA	0.70
NRI$^{>0}_{event}$	NA	NA	0.38
NRI$^{>0}_{nonevt}$	NA	NA	0.32

cf: two-sample t-test vs. Wilcoxan test

For 3 or more categories, NRI weights reclassifications indiscriminately

- For three categories, "up" can mean
  - low risk to medium risk
  - medium risk to high risk
  - low risk to high risk

NRI treats all of these the same

- For three categories, "down" can mean
  - high risk to medium risk
  - medium risk to low risk
  - high risk to low risk

NRI treats all of these the same

- When risk categories correspond to treatment decisions, the nature of reclassification matters, not just the direction

Suppose:

High risk	**Lifestyle changes + Rx**
Medium risk	Lifestyle changes
Low risk	No intervention

A new marker that moves a nonevent from "high risk" to "medium risk" improves risk prediction for that person, and that benefit is arguably greater than moving a nonevent from "medium risk" to "low risk."

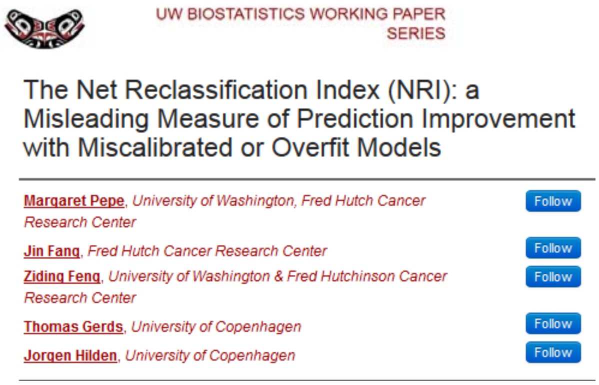
NRI counts these movements equally.

2-category NRI: new names for existing measures

- It is easy to show that for two risk categories ("low risk" and "high risk")
  - $\text{NRI}_{\text{event}}$ is the change in the True Positive rate (sensitivity)
  - $\text{NRI}_{\text{nonevent}}$ is (equivalent to) the change in the False Positive Rate (specificity)

- For 2-categories there is also a weighted NRI, wNRI, that takes into account the costs/benefits of correct/incorrect classifications
  - wNRI is the same as the change in Net Benefit

$\text{NRI}^{>0}$ is not a proper scoring rule – it can make overfit or poorly calibrated models look good



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The Net Reclassification Index (NRI): a Misleading Measure of Prediction Improvement with Miscalibrated or Overfit Models

Margaret Pepe, *University of Washington, Fred Hutch Cancer Research Center* Follow

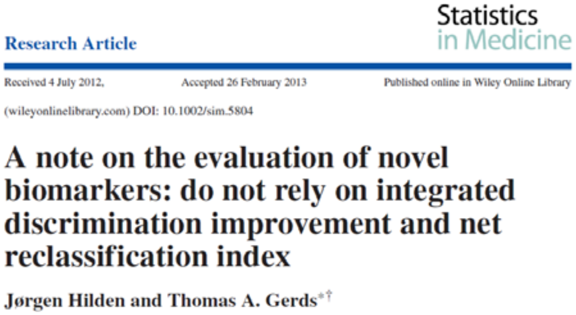
Jin Fang, *Fred Hutch Cancer Research Center* Follow

Ziding Feng, *University of Washington & Fred Hutchinson Cancer Research Center* Follow

Thomas Gerds, *University of Copenhagen* Follow

Jorgen Hilden, *University of Copenhagen* Follow

- Over-fit models for a useless new marker tend to give positive values for the NRI, even on independent data
- PMID: 26504496 PMCID: PMC4615606



Research Article

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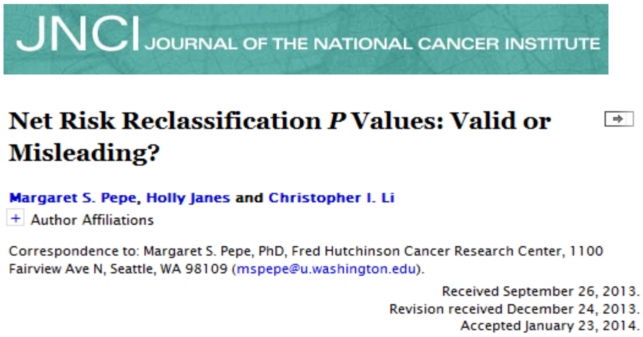
A note on the evaluation of novel biomarkers: do not rely on integrated discrimination improvement and net reclassification index

Jørgen Hilden and Thomas A. Gerds*†



JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE

Net Risk Reclassification *P* Values: Valid or Misleading?

Margaret S. Pepe, Holly Janes and Christopher I. Li

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Simulations

- X is predictive (to varying degrees)
- new marker Y is noise

Bivariate Normal Simulation Model

$$\text{Among controls: } \begin{pmatrix} X \\ Y \end{pmatrix} \sim N(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & r \\ r & 1 \end{pmatrix})$$

$$\text{Among cases: } \begin{pmatrix} X \\ Y \end{pmatrix} \sim N(\begin{pmatrix} \mu_X \\ \mu_Y \end{pmatrix}, \begin{pmatrix} 1 & r \\ r & 1 \end{pmatrix})$$

$$\operatorname{logit} P(D=1|X=x) = \operatorname{logit}(\rho) - \frac{1}{2}\mu_X^2 + \mu_X x$$

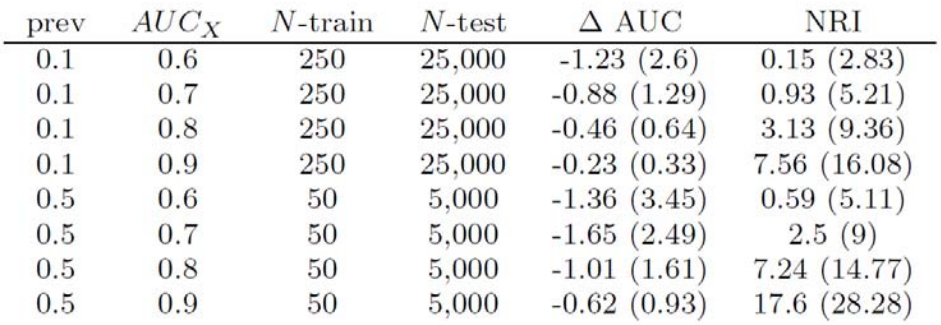
$$\operatorname{logit} P(D=1|X=x, Y=y) = \operatorname{logit}(\rho) - \frac{\mu_X^2 + \mu_Y^2 - 2r\mu_X\mu_Y}{2(1-r^2)} + \frac{\mu_X - r\mu_Y}{1-r^2}x + \frac{\mu_Y - r\mu_X}{1-r^2}y$$

In our simulations, *Y* is useless, so $\mu_Y = 0$ and $r = 0$

- Performance of model with useless marker added: ΔAUC is negative, on average

prev	AUC_X	N-train	N-test	Δ AUC	NRI
0.1	0.6	250	25,000	-1.23 (2.6)	
0.1	0.7	250	25,000	-0.88 (1.29)	
0.1	0.8	250	25,000	-0.46 (0.64)	
0.1	0.9	250	25,000	-0.23 (0.33)	
0.5	0.6	50	5,000	-1.36 (3.45)	
0.5	0.7	50	5,000	-1.65 (2.49)	
0.5	0.8	50	5,000	-1.01 (1.61)	
0.5	0.9	50	5,000	-0.62 (0.93)	

- Performance of model with useless marker added: NRI$^{>0}$ is positive, on average



prev	AUC_X	N-train	N-test	Δ AUC	NRI
0.1	0.6	250	25,000	-1.23 (2.6)	0.15 (2.83)
0.1	0.7	250	25,000	-0.88 (1.29)	0.93 (5.21)
0.1	0.8	250	25,000	-0.46 (0.64)	3.13 (9.36)
0.1	0.9	250	25,000	-0.23 (0.33)	7.56 (16.08)
0.5	0.6	50	5,000	-1.36 (3.45)	0.59 (5.11)
0.5	0.7	50	5,000	-1.65 (2.49)	2.5 (9)
0.5	0.8	50	5,000	-1.01 (1.61)	7.24 (14.77)
0.5	0.9	50	5,000	-0.62 (0.93)	17.6 (28.28)

MESA example: Polonsky et al, JAMA 2010 Adding CACS to Framingham risk factors to predict CHD events

•Risk categories 0-3%, 3-10%, >10%

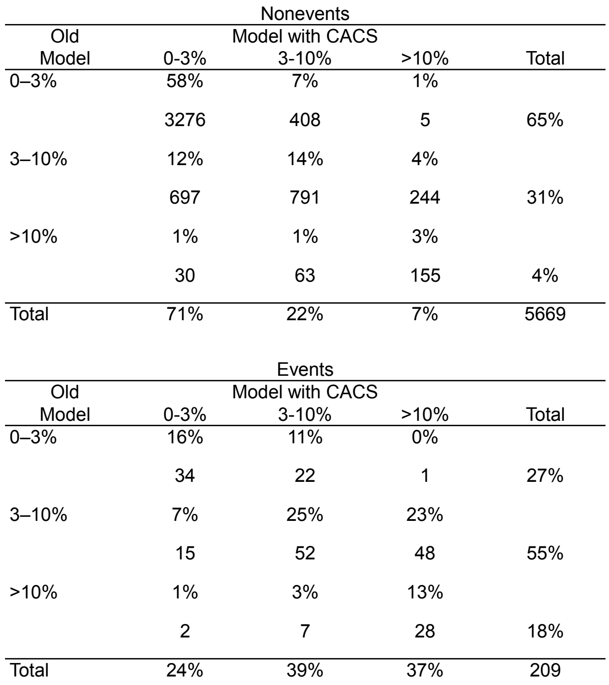
•model with CACS reclassifies 26% of the sample

estimated 3-category NRI$_{event}$ = 0.23

estimated 3-category NRI$_{nonevent}$= 0.02

These are summaries of the reclassification tables (next slide)

•How do we interpret these NRIs? Do they help us understand the clinical or public health benefit of incorporating CACS into the model?

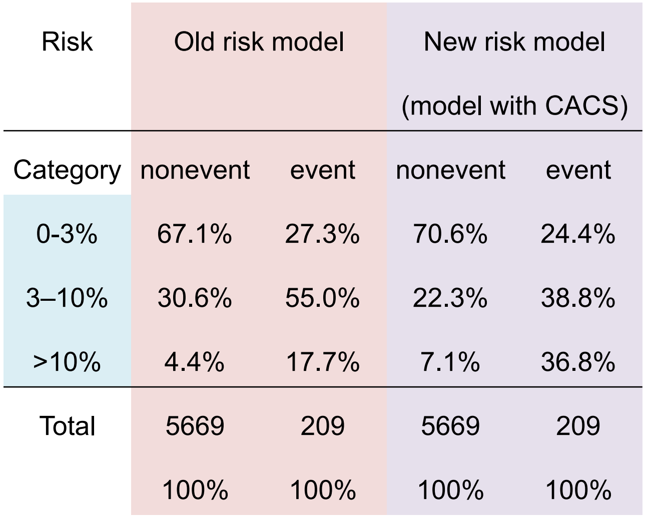


Nonevents

Old Model	Model with CACS 0-3%	 3-10%	 >10%	 Total
0–3%	58%	7%	1%	
	3276	408	5	65%
3–10%	12%	14%	4%	
	697	791	244	31%
>10%	1%	1%	3%	
	30	63	155	4%
Total	71%	22%	7%	5669

Events

Old Model	Model with CACS 0-3%	 3-10%	 >10%	 Total
0–3%	16%	11%	0%	
	34	22	1	27%
3–10%	7%	25%	23%	
	15	52	48	55%
>10%	1%	3%	13%	
	2	7	28	18%
Total	24%	39%	37%	209



Risk	Old risk model		New risk model (model with CACS)	
Category	nonevent	event	nonevent	event
0-3%	67.1%	27.3%	70.6%	24.4%
3–10%	30.6%	55.0%	22.3%	38.8%
>10%	4.4%	17.7%	7.1%	36.8%
Total	5669	209	5669	209
	100%	100%	100%	100%

Summary

- The best way to compare two risk models is to compare them on a meaningful measure of performance
  - e.g. Net Benefit of using the risk model to recommend treatment
- The same principle applies to assessing the incremental contribution of a new marker Y to risk prediction: is the performance of risk(X,Y) better than the performance of risk(X)?
- Often $AUC_{X,Y}$ will not be much larger than AUC_X. This is not because AUC is "insensitive." It is hard to improve prediction once a modest level is achieved.

Summary

- NRI statistics do not help us assess the incremental value of new markers
  - despite ~3000 citations of original 2008 paper
- Some NRI statistics are re-named versions of existing measures
- Category-free NRI has many of the same problems as ΔAUC, and some new problems
  - hard to interpret
  - potential to mislead and make useless new markers look promising
- In addition (not discussed), for NRI cannot rely on p-values or confidence intervals from published formulas

Additional Reference

- Kerr, Wang, Janes, McClelland, Psaty, Pepe: Net reclassification indices for evaluating risk prediction instruments: a critical review. *Epidemiology*, 2014.